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## Cation shifts as markers in neurodegenerative diseases

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## S U M M A R Y

The clinical syndrome of dementia is best defined as an - usually at advanced age - acquired global impairment of intellect, memory and personality, but without impairment of consciousness. Prominent causes of dementia are certain intrinsic degenerative diseases of the brain. The most common of these diseases is Alzheimer's disease (AD). The pathological hallmark of AD is the presence of large amounts of so called plaques - extracellular structures which involve processes of different neurons - and neurofibrillary tangles in nerve cell bodies of the cerebral cortex, hippocampus, amygdala and some subcortical brain areas. The next most common cause of dementia is multi-infarct dementia (MID), which can develop as a result of small strokes. In both AD and MID the temporal cortex and hippocampus are the most vulnerable brain areas. The final diagnosis for AD or MID can only be made post mortem, after careful pathological examination of the brain. Dementia is also one of the symptoms in the end stage of Huntington's disease (HD). HD is a not very common, hereditary, neurological disease. A specific class of neurons of the basal ganglia degenerates in HD brains. There are no successful drug therapies for these neurodegenerative diseases and the prognosis is still hopeless. In the first part of chapter 1 clinical, pathological and neurochemical features of AD, MID and HD are briefly reviewed.

Clinically, it is often very difficult to differentiate between depressions - a very common psychiatric disorder in old people - and dementias. Brain images produced by CT, NMR or PET techniques may provide useful information for diagnostic purposes. Using the present brain imaging techniques abnormalities in HD brains are only visible after that clinical symptoms have emerged and the striatum has been severely disrupted. More sensitive techniques to measure degeneration processes in living brain must be developed in order to a) enable early diagnosis and b) investigate the effect of drug therapies on the degenerative process. Both for brain imaging purposes as for biochemical assays on post mortem brain tissue of different psychiatric and neurological diseases a sensitive marker for cell death is badly needed. In the present thesis it is described that regional cation changes are very worthwhile for this purpose.

From experimental animals it is known that a major part of the nerve cells in the cortex, hippocampus and basal ganglia use amino acids, such as

glutamate (Glu) and  $\gamma$ -aminobutyric acid (GABA), as transmitters. GABA is produced exclusively in certain nerve cells, but Glu is present in all brain cells as a result of basal metabolism. Neurons, which use Glu as a transmitter contain much higher concentrations of the amino acid than other cells. Therefore, tissue levels of amino acids can be used as markers for the integrity of specific neurons. The second part of chapter 1 reviews some animal models for the above mentioned neurodegenerative diseases. Specific neurotoxins, such as kainic acid (KA), which is a structural analogue of Glu, produce selective lesions after local intracerebral administration. In experimental brain damage (chapters 5 and 6) not only transmitter levels are changed, but also ion contents: trauma, ischemia or intoxication of neural tissue causes increases in sodium (Na) and calcium (Ca) and decreases in potassium (K) and magnesium (Mg) levels (see chapter 1, part 3).

In chapters 2, 3 and 4 cation and amino acid contents in HD, AD, MID and age-matched control brains are described. Post mortem obtained tissue was provided by the Brain Tissue Bank, Cambridge, England (U.K.). In HD basal ganglia Na was significantly increased and K significantly decreased. GABA was remarkably decreased in the HD putamen and substantia nigra. GABA and cation levels were highly correlated. Also in AD and MID hippocampus highly increased Na and decreased K levels were found. Cation changes in the frontal cortex of the HD, AD and MID groups did not reach significance in most cases. Two different AD groups, one of 12 and one of 6 subjects, have been analyzed. In the largest group Glu was significantly decreased in the hippocampus and was highly correlated with Na/K changes. Thus, major cation shifts were observed in the pathologically most affected brain areas. The correlations with the amino acid transmitters suggest a loss of striatal GABA-ergic neurons in HD and of hippocampal glutamatergic neurons in some AD patients. In most cases Ca levels were normal in HD, AD and MID brains. Hippocampal cation changes were significantly correlated with the dementia score, obtained within one year before death. This corroborates the important role of the hippocampus in learning and memory.

The time between death and freezing of the brain tissue, e.g. post mortem delay, was in our cases often longer than 24 hours. In chapter 5 the effect of such a long post mortem delay on cations and amino acids has been investigated. This effect was measured in intact and in kainate affected brain tissue of the rat. Differences between healthy and diseased (KA) tissue diminished rapidly as post mortem delay increased. These results suggest that

in neurodegenerative diseases the elevated Na/K ratio is much more pronounced in vivo than observed post mortem. Glu appeared to be stable post mortem, whereas GABA increased in the striatum and decreased in the substantia nigra post mortem.

Chapter 6 describes visualization of the degeneration of neurons and their processes by radioactive divalent cations. It is shown by autoradiography that during a particular phase of the degeneration process radioactive calcium accumulates in the cell. Calcium has no suitable isotope for positron emission tomography (PET), but cobalt (Co) can be used as a marker for calcium and the positron emitting isotope  $^{55}\text{Co}$  has many clinical advantages, such as a half life of 17.5 hours. KA lesions of the cat forebrain could be imaged by PET using  $^{55}\text{CoCl}_2$  as a tracer. PET using this radiolabel is supposed to yield information, which can not be provided by the more traditional brain scans. This technique is probably very useful for early diagnosis of acute brain damage due to trauma, stroke, heart attack, or heart or brain surgery.

In the final chapter the possibilities of in vivo brain imaging by PET using  $^{55}\text{CoCl}_2$  and by sodium nuclear magnetic resonance imaging for localizing recent and older brain lesions are summarized. Furthermore, the latest news on the excitotoxic hypothesis for degenerative processes in AD and HD and future drug strategies are briefly addressed.